

PS-OC Quarterly Newsletter, July 2013

A physical sciences network characterization of non-tumorigenic and metastatic cells. The Physical Sciences - Oncology Centers Network. Scientific Reports 2013; 3:1449.

www.nature.com/srep/2013/130422/srep01449/full/srep01449.html

Keywords: cell biology, transnetwork

- This work provides a multifaceted description of cellular parameters of two widely used cell lines and demonstrates the value of the PS-OC Network approach for integration of diverse experimental observations to elucidate the phenotypes associated with cancer metastasis. The White House's blog recently highlighted this paper.

Growth and form of melanoma cell colonies. Baraldi MM, Alemi AA, Sethna JP, Caracciolo S, La Porta CAM, Zapperi S. Journal of Statistical Mechanics-Theory and Experiment 2013:P02032.

<http://iopscience.iop.org/1742-5468/2013/02/P02032>

Keywords: melanoma, kinetic growth processes, pattern formation, mathematical modeling

- Crystal violet assays are ways of finding clusters grown from individual cells. The size distribution of these clusters tells us information about the heterogeneity of the cell population, and the shape distributions tell us about the growth process.

Characterizing deformability and surface friction of cancer cells. Byun S, Son S, Amodei D, et al. Proc Natl Acad Sci U S A. 2013;110(19):7580-7585.

<http://www.pnas.org/content/110/19/7580.full>

Keywords: cell mechanics, cell stiffness, biophysics, suspended microchannel resonator, biosensors

Functional interplay between the cell cycle and cell phenotypes. Chen W, Wu P, Phillip JM, et al. Integrative Biology 2013; 5(3):523-534.

<http://pubs.rsc.org/en/Content/ArticleLanding/2013/IB/c2ib20246h>

Keywords: assay development, cell cycle, microscopy, single cell assay

Impact of diffusion barriers to small cytotoxic molecules on the efficacy of immunotherapy in breast cancer. Das H, Wang Z, Niazi MKK, et al Plos One 2013; 8(4).

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0061398>

Keywords: mathematical modeling, breast cancer, immunotherapy

Self-organization and entropy reduction in a living cell. Davies PCW, Rieper E, Tuszynski JA. BioSystems 2013; 111(1):1-10.

<http://www.sciencedirect.com/science/article/pii/S0303264712001888>

Keywords: mathematical modeling, Genetic code, entropy, thermodynamics, information theory

Aberration in DNA methylation in B-cell lymphomas has a complex origin and increases with disease severity. De S, Shaknovich R, Riester M, et al. Plos Genetics 2013; 9(1):e1003137.

<http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1003137>

Keywords: lymphoma, epigenetics

Breast fibroblasts modulate early dissemination, tumorigenesis, and metastasis through alteration of extracellular matrix characteristics. Dumont N, Liu B, Defilippis RA, et al. Neoplasia 2013; 15(3):249-62.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3593149/>

Keywords: malignancy, microenvironment, breast cancer

- There is still relatively little known about how signals from the microenvironment contribute to the early events in the progression to malignancy. To address this question, we used a premalignant mammary model to examine how fibroblasts, and the extracellular matrix (ECM) proteins they secrete, influence progression to malignancy. We found that carcinoma-associated fibroblasts, and the distinct aligned ECM they deposit, can cause both premalignant and malignant mammary epithelial cells to assume a mesenchymal morphology that is associated with increased dissemination and metastasis, while benign reduction mammoplasty fibroblasts favor the maintenance of an epithelial morphology and constrain early dissemination, tumor growth, and metastasis. Our results suggest that normalizing the organization of the ECM could be effective in limiting systemic dissemination and tumor growth.

An integrated computational/experimental model of lymphoma growth. Frieboes HB, Smith BR, Chuang Y, et al. Plos Computational Biology 2013; 9(3):e1003008.

<http://www.ploscompbiol.org/article/info%3Adoi%2F10.1371%2Fjournal.pcbi.1003008>

Keywords: lymphoma, computational modeling

Reconstitution of hemisomes on budding yeast centromeric DNA. Furuyama T, Codomo CA, Henikoff S. Nucleic Acids Res. 2013; 41(11):5769-83.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3675498>

Keywords: DNA physics, nucleosomes

- We show that stable yeast CenH3 hemisomes (half nucleosomes) can be reconstituted on an ~80-bp Centromere DNA Element CDEII, reconciling *in vitro* with *in vivo* observations. We propose that CDEII DNA stiffness evolved to favor Cse4 hemisome over octasome formation.

Phenotypic switch in blood: effects of pro-inflammatory cytokines on breast cancer cell aggregation and adhesion. Geng Y, Chandrasekaran S, Hsu J, Gidwani M, Hughes AD, King MR Plos One 2013; 8(1):e54959.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3553003/>

Keywords: metastasis, breast cancer, cytokines

- Hematogeneous metastasis can occur via a cascade of circulating tumor cell adhesion events to the endothelial lining of the vasculature, i.e. the metastatic cascade. Interestingly, the pro-inflammatory cytokines IL-6 and TNF- α , which play an important role in potentiating the inflammatory cascade, are significantly elevated in metastatic breast cancer (BCa) patients. Our results indicate that plasma, IL-6, and TNF- α promote breast cancer cell growth as aggregates and induce adhesive recruitment of BCa cells on E-selectin coated surfaces under flow. We propose a mechanism that could explain the invasiveness of 'triple-negative' breast cancer cell line MDA-MB-231 via a positive feedback loop of IL-6 secretion and maintenance. Taken together, our results suggest that therapeutic approaches targeting cytokine receptors and adhesion molecules on cancer cells may potentially reduce metastatic load and improve current cancer treatments.

Hypoxia-inducible factor 1 (HIF-1) promotes extracellular matrix remodeling under hypoxic conditions by inducing P4HA1, P4HA2, and PLOD2 expression in fibroblasts. Gilkes DM, Bajpai S, Chaturvedi P, Wirtz D, Semenza GL. J Biol Chem. 2013;288(15):10819-10829.

<http://www.jbc.org/content/288/15/10819.long>

Keywords: breast cancer, metastasis, hypoxia, cell mechanics

Procollagen lysyl hydroxylase 2 is essential for hypoxia-induced breast cancer metastasis. Gilkes DM, Bajpai S, Wong CC, et al. Molecular Cancer Research 2013; 11(5):456-466.

<http://mcr.aacrjournals.org/content/11/5/456.long>

Keywords: breast cancer, metastasis, hypoxia, ECM

Collagen prolyl hydroxylases are essential for breast cancer metastasis. Gilkes DM, Chaturvedi P, Bajpai S, et al. Cancer Res. 2013; 73(11):3285-96.

<http://cancerres.aacrjournals.org/content/73/11/3285.long>

Keywords: metastasis, breast cancer

Integration and regression of implanted engineered human vascular networks during deep wound healing. Hanjaya-Putra D, Shen Y, Wilson A, et al. Stem Cells Translational Medicine 2013; 2(4):297-306.

<http://www.ncbi.nlm.nih.gov/pubmed/23486832>

Keywords: clinical, angiogenesis, tissue engineering

The effect of cell cluster size on intracellular nanoparticle-mediated hyperthermia: Is it possible to treat microscopic tumors? Hedayati M, Thomas O, Abubaker-Sharif B, et al. Nanomedicine 2013; 8(1):29-41.

<http://www.futuremedicine.com/doi/abs/10.2217/nnm.12.98>

Keywords: prostate cancer, clinical treatment, oncology

- This paper aims to compare the measured surface temperature of variable size ensembles of cells heated by intracellular magnetic fluid hyperthermia with heat diffusion model predictions. The results show that for a given intracellular nanoparticle concentration, a critical minimum number of cells was required for cytotoxic hyperthermia. Above this threshold, cytotoxicity

increased with increasing cell number. The measured surface temperatures were consistent with those predicted by a heat diffusion model that ignores intercellular thermal barriers. These results suggest a minimum tumor volume threshold of approximately 1 mm³, below which nanoparticle-mediated heating is unlikely to be effective as the sole cytotoxic agent.

Evolution and morphology of microenvironment-enhanced malignancy of three-dimensional invasive solid tumors. Jiao Y, Torquato S. Physical Review E. 2013; 87(5):052707.

<http://pre.aps.org/abstract/PRE/v87/i5/e052707>

Keywords: computer simulation, microenvironment, malignancy

- In this paper, we employed a cellular automaton (CA) model to investigate microenvironment-enhanced malignant behaviors and morphologies of *in vitro* avascular invasive solid tumors in three dimensions. We find that while strong cell-cell adhesion can suppress the invasive behavior of the tumors growing in soft microenvironments, cancer malignancy can be significantly enhanced by harsh microenvironmental conditions, such as exposure to high pressure levels. We infer from the simulation results a qualitative phase diagram that characterizes the expected malignant behavior of invasive solid tumors in terms of two competing malignancy effects: the rigidity of the microenvironment and cell-cell adhesion. This diagram exhibits phase transitions between noninvasive and invasive behaviors. We also discuss the implications of our results for the diagnosis, prognosis, and treatment of malignant tumors.

Androgen receptor-independent function of FoxA1 in prostate cancer metastasis. Jin H, Zhao JC, Ogden I, Bergan RC, Yu J. Cancer Res. 2013;73(12):3725-36.

<http://cancerres.aacrjournals.org/content/73/12/3725.long>

Keywords: prostate cancer, cell biology, genomics

- Our findings illustrate an AR-independent function of FoxA1 as a metastasis inhibitor and provide a mechanism by which recurrent FoxA1 mutations contribute to prostate cancer progression.

Focal adhesion size uniquely predicts cell migration. Kim D, Wirtz D. FASEB Journal 2013; 27(4):1351-1361.

<http://www.fasebj.org/content/27/4/1351.long>

Keywords: sarcoma, cell biology

Microfabricated collagen tracks facilitate single cell metastatic invasion in 3D. Kraning-Rush CM, Carey SP, Lampi MC, Reinhart-King CA. Integrative Biology 2013; 5(3):606-616.

<http://pubs.rsc.org/en/Content/ArticleLanding/2013/IB/c3ib20196a>

Keywords: metastasis, technique development, breast cancer

- Recent studies have shown that during metastasis cancer cells form proteolytic microtracks using matrix metalloproteinases (MMPs). Secondary cells can follow these pre-made tracks without degrading the matrix. Here, we developed a novel micropatterning technique for the

study of cancer migration within physiologically relevant microtracks which mimic the complex micro-architecture of the native extracellular matrix (ECM). Using this system, we observe cancer migration and cell interaction with the surrounding ECM fibers in real time. The microtrack environment significantly increases cell speed and invasion in both invasive and non-invasive cell types. Moreover, we find that pharmacological MMP inhibition has no obvious effect on cancer cell migration within the microtracks. These insights contribute to a more thorough understanding of the processes governing microtrack migration during metastasis, and may reveal insight into the poor clinical performance of MMP inhibitors.

DNA replication timing and higher-order nuclear organization determine single-nucleotide substitution patterns in cancer genomes. Liu L, De S, Michor F. Nature Communications 2013; 4:1502. <http://www.nature.com/ncomms/journal/v4/n2/full/ncomms2502.html>

Keywords: genomics, bioinformatics, oncology

Minimization of thermodynamic costs in cancer cell invasion. Liu L, Duclos G, Sun B, et al. Proc Natl Acad Sci U S A. 2013; 110(5):1686-1691. <http://www.pnas.org/content/110/5/1686.full.pdf>

Keywords: breast cancer, metastasis

- We show that MDA-MB-231 metastatic breast cancer cells cooperatively invade a 3D collagen matrix while following a glucose gradient. The invasion front of the cells is a dynamic one, with different cells assuming the lead on a time scale of 70 h. The front cell leadership is dynamic presumably because of metabolic costs associated with a long-range strain field that precedes the invading cell front, which we have imaged using confocal imaging and marker beads imbedded in the collagen matrix. We suggest this could be a quantitative assay for an invasive phenotype tracking a glucose gradient and show that the invading cells act in a cooperative manner by exchanging leaders in the invading front.

Coordinate transcriptional and translational repression of p53 by TGF-beta1 impairs the stress response. Lopez-Diaz FJ, Gascard P, Balakrishnan SK, et al. Mol Cell 2013; 50(4):552-64. <http://www.sciencedirect.com/science/article/pii/S1097276513003341>

Keywords: breast cancer, cell biology

- We have uncovered a survival mechanism that occurs in breast cells that have just turned premalignant cells on the cusp between normalcy and cancerous. In this Molecular Cell study, we report that a protein known as transforming growth factor beta (TGF- β), considered a tumor suppressor in early cancer development, can actually promote cancer once a cell drifts into a pre-cancerous state.

High-throughput secretomic analysis of single cells to assess functional cellular heterogeneity. Lu Y, Chen JJ, Mu L, et al. Anal Chem. 2013; 85(4):2548-2556. <http://pubs.acs.org/doi/abs/10.1021/ac400082e>

Keywords: instrumentation development, protein analysis, single cell analysis

Elucidating mechanical transition effects of invading cancer cells with a subnucleus-scaled microfluidic serial dimensional modulation device. Mak M, Reinhart-King CA, Erickson D. Lab on a Chip 2013; 13(3):340-348.

<http://pubs.rsc.org/en/content/articlelanding/2013/LC/c2lc41117b>

Keywords: metastasis, cell mechanics, breast cancer

- Here we introduce a device and metric to assess cell transition effects across mechanical barriers. Our results demonstrate that dimensional modulation in confined spaces with mechanical barriers smaller than the cell nucleus can induce distinct invasion phases and elongated morphological states.

Tuning three-dimensional collagen matrix stiffness independently of collagen concentration modulates endothelial cell behavior. Mason BN, Starchenko A, Williams RM, Bonassar LJ, Reinhart-King CA. Acta Biomaterialia 2013; 9(1):4635-4644.

<http://www.sciencedirect.com/science/article/pii/S1742706112003741>

Keywords: angiogenesis, cell mechanics

- Using collagen-based scaffolds with tuneable mechanical properties, we show that endothelial cells embedded in the matrix demonstrate increased spreading, angiogenic sprouts, and spheroid outgrowth with increasing matrix stiffness. Differences in sprout length are maintained even when the receptor for advanced glycation end products is inhibited. Our results demonstrate the ability to de-couple matrix stiffness from matrix density and structure in collagen gels, and that increased matrix stiffness results in increased sprouting and outgrowth.

Spreaders and sponges define metastasis in lung cancer: a Markov chain Monte Carlo mathematical model. Newton PK, Mason J, Bethel K, et al. Cancer Res. 2013; 73(9):2760-2769.

<http://cancerres.aacrjournals.org/content/73/9/2760>

Keywords: mathematical modeling, metastasis, lung cancer

- A Markov chain Monte Carlo mathematical approach can determine a pathway diagram that classifies metastatic tumors as "spreaders" or "sponges" and orders the timescales of progression from site to site. In light of recent experimental evidence highlighting the potential significance of self-seeding of primary tumors, we use a Markov chain Monte Carlo (MCMC) approach, based on large autopsy data sets, to quantify the stochastic, systemic, and often multidirectional aspects of cancer progression.

Epidermal growth factor receptor tyrosine kinase inhibitor-resistant disease. Ohashi K, Maruvka YE, Michor F, Pao W. Journal of Clinical Oncology 2013; 31(8):1070-1080.

<http://jco.ascopubs.org/content/31/8/1070.long>

Keywords: lung cancer, oncology, EGFR

Epigenetic therapy of hematological malignancies: where are we now? Popovic R, Shah MY, Licht JD. Therapeutic advances in hematology 2013; 4(2):81-91.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3629753/>

Keywords: epigenetics, genomics

- This review will summarize the progress made using the currently available epigenetic therapies and discuss some of the more recently identified targets whose inhibition may present potential avenues for the treatment of hematologic malignancies.

Rare somatic cells from human breast tissue exhibit extensive lineage plasticity. Roy S, Gascard P, Dumont N, et al. Proc Natl Acad Sci U S A. 2013; 110(12):4598-4603.

<http://www.pnas.org/content/110/12/4598.full.pdf>

Keywords: breast cancer, cell biology

- We identified cell surface markers associated with repression of p16 (INK4a)/cyclin-dependent kinase inhibitor 2A (CDKN2A), a critical determinant in the acquisition of a plastic state. These cell surface markers allowed direct isolation of rare cells from healthy human breast tissue that exhibit extensive lineage plasticity. This subpopulation is poised to transcribe plasticity markers, OCT3/4, SOX2, and NANOG, at levels similar to those measured in human embryonic stem cells and to acquire a plastic state sensitive to environmental programming. *In vitro*, *in vivo*, and teratoma assays demonstrated that either a directly sorted (uncultured) or a single-cell (clonogenic) cell population from primary tissue can differentiate into functional derivatives of each germ layer, ectodermal, endodermal, and mesodermal. In contrast to other cells that express OCT3/4, SOX2, and NANOG, these human endogenous plastic somatic cells are mortal, express low telomerase activity, expand for an extensive but finite number of population doublings, and maintain a diploid karyotype before arresting in G1.

Suppression of miRNA-708 by polycomb group promotes metastases by calcium-induced cell migration. Ryu S, McDonnell K, Choi H, et al. Cancer Cell 2013; 23(1):63-76.

<http://www.sciencedirect.com/science/article/pii/S1535610812005089>

Keywords: metastasis, breast cancer, cell biology

- Patients with triple-negative breast cancer (TNBC) have the worst outcome among patients with breast cancer due to high propensity for recurrence and metastatic spread. Furthermore, to our knowledge, there is no approved targeted therapy for treatment of TNBC. Here, we show that the expression of miR-708 is reduced during metastatic progression of breast cancer. We demonstrate that polycomb repressor complex 2-mediated suppression of miR-708 increases expression of neuronatin, which elevates intracellular Ca²⁺ levels to promote cell migration and metastasis formation. Together, these findings support the notion that miR-708 is a potential therapeutic against metastatic breast cancer.

Advocacy spurs innovation: promoting synergy between physical and biomedical sciences. Samson S, Acerbi I, Baas C, Weaver V, Rugo H. EPJ Nonlinear Biomedical Physics 2013, 1:1 (9 May 2013).

<http://www.epjnonlinearbiomedphys.com/content/pdf/epjnbp1.pdf>

Keywords: advocacy

- Fellow AIS member, Susan Samson, has co-written a research advocacy article recently published in EPJ Nonlinear Biomedical Physics. This commentary draws on the experiences of the Bay Area PS-OC, one of the twelve centers funded by the NCI, and explores the way physical

scientists, clinical researchers, and advocates work together in a transdisciplinary setting to optimize innovative and needed paradigm shifts in breast cancer research and treatment. Focusing on the intersections of mechanobiology research and advocacy involvements, we identify strategies for leveraging collaborative engagement, describe some of the tensions and challenges in the process, consider the implications of such involvements for the conduct of biomedical research, and connect the PS-OC's programmatic work to emerging policy concerns. Ultimately, this is a call to action for the cancer research community. This call to action emphasizes a process for building team collaboration, and it argues for the importance of advocacy integration within transdisciplinary physical sciences and oncology research teams to help disrupt the status quo, spur on medical innovation, and reshape the conduct of biomedical research.

Physiological levels of blood coagulation factors IX and X control coagulation kinetics in an *in vitro* model of circulating tissue factor. Tormoen GW, Khader A, Gruber A, McCarty OJT. *Physical biology* 2013; 10(3):036003-036003.

<http://iopscience.iop.org/1478-3975/10/3/036003/>

Keywords: thrombosis, clinical, cancer

- The mechanism behind thrombosis in cancer may be circulating tissue factor (TF), as levels of circulating TF are associated with thrombosis.

Perivascular cells in blood vessel regeneration. Wanjare M, Kusuma S, Gerecht S. *Biotechnology Journal* 2013; 8(4).

<http://onlinelibrary.wiley.com/doi/10.1002/biot.201200199/abstract;jsessionid=7F0DDAC4F2A03C6A5677590473D8EDCE.d01t03>

Keywords: tissue engineering, vascular engineering, angiogenesis

Interstitial friction greatly impacts membrane mechanics. Wirtz D. *Biophys J.* 2013; 104(6):1217-1218.

<http://www.sciencedirect.com/science/article/pii/S0006349513001884>

Keywords: cell mechanics, review

The effect of interstitial pressure on tumor growth: Coupling with the blood and lymphatic vascular systems. Wu M, Frieboes HB, McDougall SR, Chaplain MAJ, Cristini V, Lowengrub J. *J Theor Biol.* 2013;320:131-151.

<http://www.sciencedirect.com/science/article/pii/S0022519312006200>

Keywords: computational model, angiogenesis, tumor growth

Doxorubicin enhances nucleosome turnover around promoters. Yang F, Kemp CJ, Henikoff S. *Current Biology* 2013; 23(9):782-787.

<http://www.cell.com/current-biology/fulltext/S0960-9822%2813%2900345-X>

Keywords: chemotherapeutics, cell biology

- We find that doxorubicin enhances nucleosome turnover around gene promoters and that turnover correlates with gene expression level. Our results suggest that anthracycline

intercalation promotes nucleosome turnover around promoters by its effect on DNA topology, with possible implications for mechanisms of cell killing during cancer chemotherapy.

A dynamic structural model of expanded RNA CAG repeats: a refined X-ray structure and computational investigations using molecular dynamics and umbrella sampling simulations. Yildirim I, Park H, Disney MD, Schatz GC. J Am Chem. Soc. 2013; 135(9):3528-3538.

<http://pubs.acs.org/doi/abs/10.1021/ja3108627>

Keywords: RNA, computational modeling

- Unstable CAG repeats are associated with cancer while expansion of these repeats cause different neurodegenerative disorders. We solved a crystal structure of a model RNA CAG repeat, and did extensive computational study to understand the dynamics of 1x1 AA internal loops in RNA CAG repeats. We found that 1x1 AA internal loops in RNA CAG repeats are dynamic and can prefer multiple different conformations.

Regulation of nucleosome dynamics by histone modifications. Zentner GE, Henikoff S. Nature Structural & Molecular Biology 2013; 20(3):259-266.

<http://www.nature.com/nsmb/journal/v20/n3/full/nsmb.2470.html>

Keywords: review, histones, cell biology

- Histone modifications are linked to essentially every cellular process requiring DNA access, including transcription, replication and repair. In this review, we consider properties of the major types of histone modification in the context of their associated biological processes to view them in light of the cellular mechanisms that regulate nucleosome dynamics.

ISWI and CHD chromatin remodelers bind promoters but act in gene bodies. Zentner GE, Tsukiyama T, Henikoff S. Plos Genetics 2013; 9(2):e1003317.

<http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1003317>

Keywords: genomics, transcription

- ISWI and CHD ATP-dependent chromatin remodelers act in gene bodies, however we find that they are also highly enriched at nucleosome-depleted regions (NDRs), where they bind to extended regions of DNA adjacent to particular transcription factors. We suggest that remodelers act on regions of transient nucleosome unwrapping or depletion within gene bodies subsequent to transcriptional elongation.